UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/722,733	11/25/2003	Dominique P. Bridon	500862001601	7359

20872 7590 12/29/2004

MORRISON & FOERSTER LLP
425 MARKET STREET
SAN FRANCISCO, CA 94105-2482

EXAMINER	
LUCAS, ZACHARIAH	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 12/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/722,733	BRIDON ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11-25-2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 20-22 are pending and under consideration in the present application.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on November 25, 2003 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

Specification

3. The amendment filed on November 25, 2003 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the incorporation by reference of the teachings of U.S. Application 09/623,548 and the applications from which it claims priority. The teachings of these applications are broader in scope (relating to the modification and stabilization of proteins in general) than the teachings of the current application as filed and its parent cases through U.S. Application 10/288,340 (the teachings of which are limited to the modification of certain insulinotropic peptides).

It is noted that the incorporation by reference was made in a preliminary amendment filed with the present application. However, this application is a continuation of 10/288,340 and 09/657,332, and the Oath/Declaration filed with this application is the Declaration filed in the

09/657,332 application. The teachings of Application 09/623,548 and the applications from which it claims priority were not incorporated by reference into the 09/657,332 application. Because the material incorporated by reference into the present application was incorporated after the execution of the Oath/Declaration, and was not referred to by the Oath/Declaration filed in the present application, the newly incorporated material is New Matter to the present application.

Applicant is required to cancel the new matter in the reply to this Office Action.

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. **The Applicant has not provided a paper copy of the sequence listing in the present application, or a statement that the sequence listing in the present application is identical to the CRF listing submitted in the parent application**. It is noted that the Applicant filed with the present application a request to transfer both the paper and CRF listings from the parent application to the current application. While the CRF listing from the parent has been incorporated into the present application, there is no procedure for the copying of the paper copy into a later filed application. See e.g., MPEP 2422.05 (discussing the transfer of the CRF copy, and noting reference to a paper copy of the listing submitted in the later filed application).

Applicant is required to submit a paper copy of the sequence listing in the present application along with the statement regarding identity between the previously submitted CRF and the paper copy submitted in the present application in the response to this action.

5. The specification is objected to for containing referring to sequences without also identifying them by the sequence identifier assigned to them in the sequence listing as required by 37 CFR 1.821(d). See e.g., p. 47, lines 3-4; p. 48, lines 6-7; and p. 49, lines 8-9. These are only a few instances of the lack of sequence identification. The examiner would like to bring the applicant's attention to the following excerpt from MPEP §2422.03:

> 37 CFR 1.821(d) requires the use of the assigned sequence identifier in all instances where the description or claims of a patent application discuss sequences regardless of whether a given sequence is also embedded in the text of the description or claims of an application. This requirement is also intended to permit references, in both the description and claims, to sequences set forth in the "Sequence Listing" by the use of assigned sequence identifiers without repeating the sequence in the text of the description or claims. Sequence identifiers can also be used to discuss and/or claim parts or fragments of a properly presented sequence. For example, language such as "residues 14 to 243 of SEQ ID NO: 23" is permissible and the fragment need not be separately presented in the "Sequence Listing." Where a sequence is embedded in the text of an application, it must be presented in a manner that complies with the requirements of the sequence rules.

The applicant is therefore required to amend the specification to comply with 37 CFR 1.821(d).

Double Patenting

6. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

7. Claims 20 and 22 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1 and 2 of prior U.S. Patent No. 6,514,500. This is a double patenting rejection.

8. Claims 20 and 21are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 20 and 38 of copending Application No. 10/288,340 (which is an allowed application). This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claim 21 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 6,514,500. Although the

conflicting claims are not identical, the claims of the patent would anticipate the presently claimed invention if applied as prior art. The claim is therefore rejected for double patenting.

11. Claim 22 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over c claims 20 and 38 of copending Application No. 10/288,340 (which is an allowed application). Although the conflicting claims are not identical, the claims of the copending application would anticipate the presently claimed invention if applied as prior art. The claim is therefore provisionally rejected for double patenting.

12. Claims 20-22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3, 4, 6, 8, 13, and 14 of U.S. Patent No. 6,329,336. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the patent are generic to the presently claimed derivatives of the GLP-1 peptide. These GLP-1 derivatives are derivatives of the peptide disclosed as SEQ ID NO: 17 in the patent. Further, the modifications of the presently claimed peptides are either disclosed in, or obvious from the disclosure in, the patent. See e.g., column 3, lines 10-20, and column 8, lines 35-55; and Example 9. The combination of the peptides with a pharmaceutically acceptable carrier is not explicitly disclosed by the patent, however, as the patent teaches methods of administering the peptide derivatives to patients, and as such methods of administration are known generally in the art to involve the use of pharmaceutically acceptable carriers, this

limitation is also obvious over the patent. Thus, the presently claimed methods are obvious species of the genus described by identified claims of the 6,329,336 patent.

13. Claims 20-22 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 20-23 of copending Application No. 10/722,099. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application, which describe a conjugate comprising the Glucagon-like peptide (GLP) in claim 20 of the present application, is a species within the present claims. Because the claims of the copending application would anticipate the current claims if the copending application qualified as prior art, the claims of the present application are rejected for obviousness type double patenting.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. Claims 20-22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 12-17, and 21-29 of U.S. Patent 6,593,295. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application are generic to the currently claimed peptide conjugates. Although the claims in the co-pending application do not specifically identify the presently claimed compounds (they do not teach the D-Ala derivation), the independent claims of the patent are generic to it. Further, patent teaches the making of the D-

Alanine GLP-1 derivatives. See e.g., columns 34-38. The currently claimed conjugates are therefore obvious variants of the previously claimed compositions.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not (yet) in fact been patented.

15. The above rejection is, in part, based on the specification of a previously issued patent, rather than the claims. In support of the use of this material, the examiner notes the following excerpt from MPEP section 804:

> When considering whether the invention defined in a claim of an application is an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art. This does not mean that one is precluded from all use of the patent disclosure.
>
> The specification can always be used as a dictionary to learn the meaning of a term in the patent claim. In re Boylan, 392 F.2d 1017, 157 USPQ 370 (CCPA 1968). Further, those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. In re Vogel, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970). The court in Vogel recognized "that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim," but that one can judge whether or not the invention claimed in an application is an obvious variation of an embodiment disclosed in the patent which provides support for the patent claim. According to the court, one must first "determine how much of the patent disclosure pertains to the invention claimed in the patent" because only "[t]his portion of the specification supports the patent claims and may be considered." The court pointed out that "this use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 35 U.S.C. 103, since only the disclosure of the invention claimed in the patent may be examined."

Thus, the courts have held that it is permissible to use the specification in determining what is included in, and obvious from, the invention defined by the claim on which the rejection is based. This is true even where elements are drawn from the specification describing the claimed invention which are not elements in the claim itself.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Larsen et al. (U.S. Patent 6,528,486 – Larsen); in view of Pouletty et al. (U.S. Patent 5,612,034- Pouletty), Krantz et al. (U.S. Patent 6,107,489- Krantz), and Hyldig-Nielson (U.S. Patent 5,612,458); and in view of Marburg et al. (Bioconjugate Chemistry, 7:612-616), and Siegel et al. (Regulatory Peptides, Vol. 79, pp. 93-102, mailed from publisher on Feb. 22, 1999- hereinafter Siegel). The rejected claims read GLP-1(7-36) derivatives comprising a D-alanine in the position of residue 8, a Lysine added to the C-terminal of the peptide and conjugated via the lysine to a maleimidopropionic acid (MPA), to conjugates of the derivative to a blood protein, and to pharmaceutical compositions comprising these derivatives and conjugates. The peptides are conjugated to MPA through a 2-(2-amino)ethoxy]ethoxy acetic acid (AEEA) linker molecule.

Larson teaches both a D-Ala^{8}- GLP-1(7-36) and the addition of a Lysine in position 37 such that non-peptide groups may be attached thereto. Column 3, line 66 to column 4, line 4, and column 6, line 60 to column 7, line 14. Larson teaches that these peptide analogs induce insulin production, and may be used in the treatment of diabetes. Column 15, lines 15-25. However, while the reference teaches both of these derivations, the reference also focuses on the use of a derivative of the alanine at position 8 with a Glycine rather than the D-Ala, and does not teach

the use of the Lysine as a binding site of MPA, or the attachment of the resultant derivative with a blood protein.

The attachment of the protein to a blood protein is rendered obvious by the teachings of Larson in combination with the Pouletty and Krantz references. Pouletty teaches the use of a two part conjugate linking a therapeutic agent to a blood component thereby extending the agents effective lifetime in the body. Col. 2, lines 5-10, and 15-40. The patent teaches that the method described may used for many therapeutic agents, including those that bind to cell surface receptors, including those to renin and insulin. Col 8, lines 3 and 11-12. Further, the patent teaches that, rather than having a two-part conjugation between the blood component and the therapeutic agent, one may put the agent on the first part, which directly attaches to the blood component. Col. 5, lines 9-36; esp. lines 34-35 stating that it is generally satisfactory to have the therapeutic agent on the first compound.

However, the Pouletty does not teach the use of MPA to attach to the blood component, or the use of the specific GLP-1(7-36) derivative with an d-isomer of alanine in position 8 and a lysine added to the C-terminal. The Krantz patent, entitled "Extended Lifetimes In Vivo Renin Inhibition," deals with the art of making chemically active proteins last for longer periods within the body by joining them to blood proteins, Column 2, lines 40-52, and column 3, lines 33-60. This conjugation can be accomplished by bonding the renin to reactive entities, compounds capable of forming covalent bonds- especially with mobile blood components. Col. 3, lines. 33-44. The patent teaches that the preferred reactive entity is member of the maleimido-containing group; and that MPA is one of the two preferred reactive groups. Col. 5, lines 51-56. Thus it is would have been obvious to one of ordinary skill in the art to combine these two references with

Larson to create a system of delivering the GLP-1 derivative with an extended in vivo effective lifetime using MPA as a reactive member to join the GLP-1 peptide with a blood protein.

Each of Krantz and Pouletty also teach that the MPA may be indirectly bound to the peptide through a linker. Krantz, columns 3-4; and Pouletty, column 3, lines 25-59. Pouletty further teaches that the linking Group used is not critical, and that any linking group may be used. Pouletty also teaches that the length of the linker is variable.

Hyldig-Nielson teaches the use of AEEA as a linker between a biotin a label and a subject molecule, and therefore that the linker was known to those in the art. As the linker is one that is known in the art, and as Pouletty teaches that any such linker may be used, it would have been obvious to one of ordinary skill in the art to use the linker as such between the MPA and the peptide of Larson. As indicated by Pouletty, the size of the linker molecule (and therefore the number of AEEA molecules) used is variable, and subject to optimization by those wishing to practice the invention. The variation between 0-2 AEEA molecules is therefore obvious as such.

None of the above references individually teach the attachment of the MPA to a Lysine added as residue 37 to the GLP-1(7-36) peptide. However, Marburg does teach the conjugation of a protein with a carrier molecule with a maleimido group. Page 612, left column. The reference further teaches that maleimido groups may be joined to either the N-terminal amino acid, or to a Lysine residue. Page 612, right column. Because this reference teaches that Lysines may be used to attach maleimido groups, and Larson teaches the addition of a C-terminal lysine on the GLP-1 peptide such that a non-peptide moiety may be added, it would have been obvious to one of ordinary skill in the art to add a Lysine to C-terminus of the D-ALA^{8} GLP-1(7-36)

suggested by Larson and taught by Siegel. Having done this, it would then have been obvious to those in the art to join this peptide to the blood proteins as suggested by Krantz and Pouletty.

While Larson teaches that a D-Ala^8 derivative of the GLP-1 may be made, none of the references suggest a motivation for doing so. The Siegel reference teaches that D-Ala^8 GLP-1(7-36) is one of 2 derivatives of GLP-1 that have the effect of lengthening the period of stimulating insulin production (from normal GLP-1) and indicated that this derivative is the only derivative with an extended in vivo half-life. P. 99. Thus, this reference suggests a motivation to one skilled in the art to use the D-ALA^8 GLP-1(7-36) in a therapeutic composition. Thus, the combined teachings of this reference and Larson would have lead one of ordinary skill in the art to make the claimed GLP-1 peptide derivative. The Larson, Siegel, Marburg, Pouletty, and Krantz references cumulatively suggest, and render obvious to the presently claimed GLP-1 derivatives.

18. It is noted that the above obviousness rejection was made in the parent application 10/288340, and was overcome by a declaration filed by the Applicant under 37 CFR 1.132. However, affidavits or declarations, such as those submitted under 37 CFR 1.131 and 37 CFR 1.132, filed during the prosecution of the parent application do not automatically become a part of this application. Where it is desired to rely on an earlier filed affidavit or declaration, the applicant should make the remarks of record in the later application and include a copy of the original affidavit or declaration filed in the parent application.

Conclusion

19. No claims are allowed.

20. The following prior art reference is made of record and is considered pertinent to applicant's disclosure as close prior art. However, the reference is not considered to anticipate or render obvious the claimed invention.

WO 98/20895, naming Knudsen et al. as inventors. This reference teaches GLP-1 derivatives, but does not teach or suggest the derivative claimed in the present application.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 703-308-4240. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Z. Lucas
Patent Examiner

JAMES HOUSEL 12/26/04
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600